THE PREPARATION OF MERCAPTOINDOLES

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ABSTRACT

2-Nitro-4-benzylmercaptotoluene was prepared from 2-nitro-4-aminotoluene by means of the conventional xanthogenic ester synthesis and subsequent benzylation. It was submitted to the Reissert indole synthesis and the resulting compound was debenzylated using sodium in liquid ammonia to yield 6-mercaptoindole. Similarly, 5-mercaptoindole was prepared from 2-nitro-5-aminotoluene. Methods of synthesis of 4- and 7- mercaptoindoles have been proposed and partially completed.

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THE PREPARATION OF MERCAPTOINDOLES

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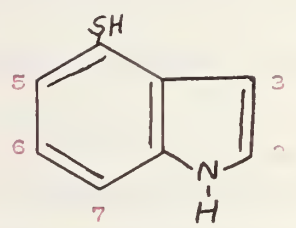
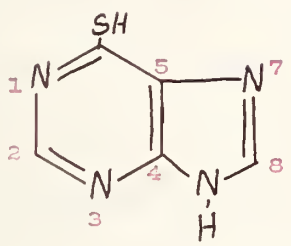
INTRODUCTION

The problem undertaken in this work was the preparation of 4-mercaptoindole (A), the indole analogue of 6-mercaptopurine (B).



A



B

In addition, it was thought of interest to prepare the 5-, 6-, and 7-mercaptoindoles, and thus make them available for physiological tests.

The interest in 4-mercaptoindole stems from the relatively recent application of 6-mercaptopurine in the treatment of leukemia. Various workers (6, 9) have shown that this compound is antagonistic to certain connective tissue cancers in mice and produces leukopenia, for a few months at least, in leukemia patients who developed resistance to ACTH and cortisone. 4-Mercaptoindole, like 6-mercaptopurine, might also exhibit antileukematic properties and thus add to our list of agents useful in cancer chemotherapy.

DISCUSSION

A number of methods for the preparation of indoles are available. Fischer's indole synthesis (17) involves the cyclization, under acidic conditions using $ZnCl_2$, $AlCl_3$, HCl, H_3PO_4, etc., of the phenylhydrazones of alkyl or alkaryl-ketones, aldehydes or ketoacids. Indole is not available by the direct application of this method, but it can be prepared by the decarboxylation of 2-carboxyindole obtained by the cyclization of the phenylhydrazone of pyruvic acid. The synthesis of indole compounds, substituted in the 2- to 7-positions inclusive, is possible by this general method.

The Japp-Klingeman reaction (25) yields phenylhydrazones, which may be cyclized to indole derivatives, by the reaction between a phenyldiazonium chloride and the sodium salt of a keto acid or the ester such as ethyl acetoacetate.

Taylor and Hobson (41) prepared indole by treating the α, β-dibromide of N-acetyl-o-aminostyrene with alcoholic potassium hydroxide.

Stephen's synthesis (40) of the indole molecule involves the reduction of o-aminophenylacetaldehyde. This method is an extension of his aldehyde synthesis, which is conducted by

passing hydrogen chloride into a mixture of an aromatic nitrile and anhydrous stannous chloride in absolute ether.

Reissert (35) prepared 2-carboxyindole by the cyclization of o-nitrophenylpyruvic acid in zinc and acetic acid. This may be converted to indole by decarboxylation.

Indoles may also be prepared by Madelung's reaction (28) which involves an intramolecular Claissen condensation of an acyl or aroyl derivative of an o-toluidine. This gives good results with the acetyl and benzoyl derivatives, but not with the formyl.

Several routes have been developed for the introduction of a mercapto group.

Treatment of a bromo- or chloro-compound with sodium or potassium hydrosulfide has, in some cases, afforded the desired thiol. Thus, Thirtle (42) prepared 2-mercaptopyridine by refluxing a mixture of potassium hydrosulfide and 2-bromopyridine in propylene glycol.

Thiourea, reacting upon a compound containing a relatively active halogen forms a thiouronium salt from which the thiol is readily available in reasonably good yields. An example of this method is the synthesis of 2-mercaptopyridine from 2-bromopyridine by Phillips and Shapiro (32).

Diazonium salts may be changed to thiols by treatment with suitable reagents. O-Tolyl-thiophenol has been prepared by

lithium aluminum hydride reduction of the xanthogenic ester prepared from potassium ethyl xanthate and the diazonium salt of o-toluidine (8). The xanthogenic ester may also be converted to the thiol by alkaline hydrolysis, but the yields are considerably less than those of the lithium aluminum hydride method.

Bardos, Herr and Enkoji (2) prepared 5-thiouracil by alkaline hydrolysis of the isothiouronium salt prepared from thiourea and diazotized 5-aminouracil, the overall yield being 17%.

The reduction of sulfonylhalides finds application in the preparation of mercaptans. A number of reducing agents have been used, including lithium aluminum hydride, zinc and hydrochloric acid and tin and hydrochloric acid. Marvel and Caesar (29) prepared 4-mercaptotoluene in 50% yield by the reduction of p-toluene sulfonyl chloride with lithium aluminum hydride. Thiophenol was prepared in 91% yield by Adams and Marvel (1) by the reduction of benzene sulfonyl chloride with zinc dust and sulfuric acid at 5-0°.

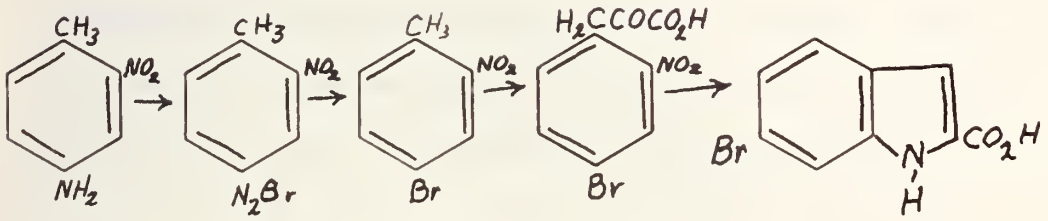
In this work, the application of a number of the above methods has been attempted involving the introduction of the mercapto group both before and after the formation of the indole nucleus.

Previous to this work, Brown and Kutney (46), in this labor-

atory, attacked the problem of synthesis of mercaptoindoles by the Fischer method. They attempted to introduce the thiol group into the molecule, before cyclization to the indole, by reduction of the appropriate nitrosulfonyl chloride. Working with m-nitrosulfonyl chloride, they failed to obtain any satisfactory product with the reducing agents zinc and sulfuric acid, tin and hydrochloric acid or iron and hydrochloric acid. However, they did succeed in introducing the mercapto group by treatment of p-nitrochlorobenzene with sodium sulfide, a reaction in which the chlorine atom was replaced by the mercapto group while, at the same time, the nitro group was reduced to the amine. The procedure used was that of Gilman and Gainer (21) but this required the modification of shortening the reaction period to prevent the formation of undesired sulfides, such as 4,4^{1}-dinitrodiphenylsulfide. In their attempts to convert the p-aminothiophenol to the p-thiophenylhydrazine, they found that diazotization of the amine was readily accomplished, but the next step of reduction of the diazonium salt with sodium sulfite failed. Reduction with stannous chloride seemed to be more effective, but they were unable to effect purification of the product.

In the continuation of this work, it was decided to attack the problem via replacement by the thiol group of a bromine atom attached to the indole nucleus using sodium or potassium hydro-

sulfide or thiourea. The first problem was the preparation of the desired bromoindoles as these were hitherto unavailable. The chloroindoles had been prepared before, the 4-chloroindole by Uhle (44) and the 5-, 6-, and 7-chloroindoles by Rydon and Long (37). These were, however, unsatisfactory as their chlorine atoms were found to be unreactive under the conditions employed. Therefore, it was hoped that the bromine atom might be more readily replaced. Reissert's method (35) as developed by Uhle, for the synthesis of indoles was first examined, since 2-carboxy-4-bromoindole had already been prepared by Barltrop and Taylor (3) by this procedure. The latter authors were unable to decarboxylate this compound. Using Barltrop and Taylor's method, 2-carboxy-6-bromoindole was prepared via the following scheme:



Decarboxylation of the carboxyindole was attempted by refluxing in quinoline containing copper powder. This gave varying results but was generally successful yielding 6-bromo-

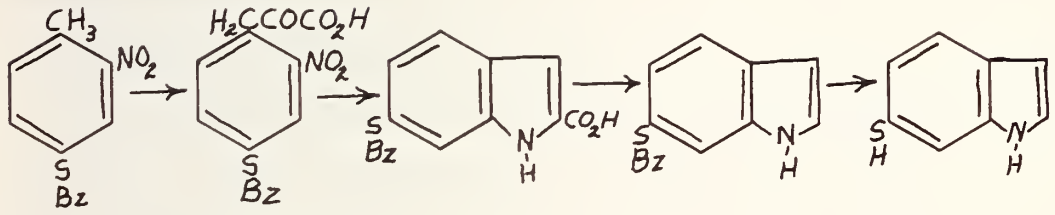
indole. The variable results exhibited by this reaction were not understood until Rydon and Tweddle (38) discovered that decarboxylation of carboxyindoles, prepared by the method of Uhle, was inhibited by the presence of sulfate which had not been completely removed after the ferrous sulfate-ammonium hydroxide reduction of the phenylpyruvic acid.

Shortly after our synthesis of 6-bromoindole, a paper was published by Plieninger (34) describing its preparation by the decarboxylation of 2-carboxy-6-bromoindole using quinoline and fused cuprous bromide.

4-Bromoindole was prepared by the same method as the 6-isomer, and was treated with thiourea as well as with potassium hydrosulfide in various solvents, such as n-propyl alcohol, absolute ethanol and ethylene glycol, but no mercaptan was isolated from the reaction mixtures. Since the treatment of 4-bromoindole had been unsuccessful, it was decided not to submit 6-bromoindole to these reactions.

It was then decided to attempt to introduce the thiol group into the molecule before the cyclization step. Blaikie and Perkin (5) have prepared methoxyindoles employing Reissert's method, so it was hoped that analogous sulfur compounds could be synthesized using similar procedures. The introduction of the thiol group into the molecule was accomplished by

diazotization of 2-nitro-4-aminotoluene, conversion to the xanthogenic ester followed by hydrolysis and the resulting thiol benzylated immediately to protect it from oxidation. The following scheme illustrates the sequence of reactions:



The preparation of 2-nitro-4-benzylmercaptophenylpyruvic acid from 2-nitro-4-benzylmercaptotoluene and diethyloxalate was accomplished using both sodium and potassium ethoxide. Since sodium ethoxide gave a good yield (80%), it was used in preference to the more dangerous method using potassium. The compound obtained from the condensation gave two of the characteristic tests for a phenylpyruvic acid; a deep-red coloration with sodium hydroxide and a dark-green coloration with alcoholic ferric chloride solution. The phenylpyruvic acid was readily cyclized to the indolecarboxylic acid by means of ferrous sulfate-ammonium hydroxide reduction followed by a difficult and tedious aqueous extraction of the product from the ferric hydroxide sludge. The carboxylic acid was carefully freed of sulfate so that the latter would not interfere with the decarboxylation.

Decarboxylation of the indolecarboxylic acid was carried out in quinoline both with and without cuprous chromite-barium chromite catalyst, the yield from the former being 50% and the latter 66%. It was also found that decarboxylation in the presence of the catalyst could be carried out at a lower temperature.

The final step in the preparation of 6-mercaptoindole was cleavage of the benzylthio ether to remove the benzyl group. Contrasted with the comparatively large amount of information that is available on the cleavage of oxygen ethers, the literature does not afford much on the cleavage of thio ethers. Burwell (7), in his review of the cleavage of ethers, devotes only one page to thio ethers. This review points out that with acidic reagents such as hydriodic acid, pyridine hydrochloride, and aluminum chloride, thio ethers are much less readily cleaved than are the oxygen ethers. On the other hand, with alkali metals, thio ethers are at least as easily cleaved as are the oxygen ethers. An exception to this general rule is that dialkyl oxygen ethers are resistant to alkali metals, whereas the sulfur analogues are readily split to form an alkyl mercaptan and an alkane . Hughes and Thompson (24) postulate that this may be due to the possibility of an electron being added to the sulfur atom, to form

R_2S^- or $R_2S^=$, which then dissociates.

$$R_2S + 2Na + NH_3 \longrightarrow RSNa + RH + NaNH_2$$

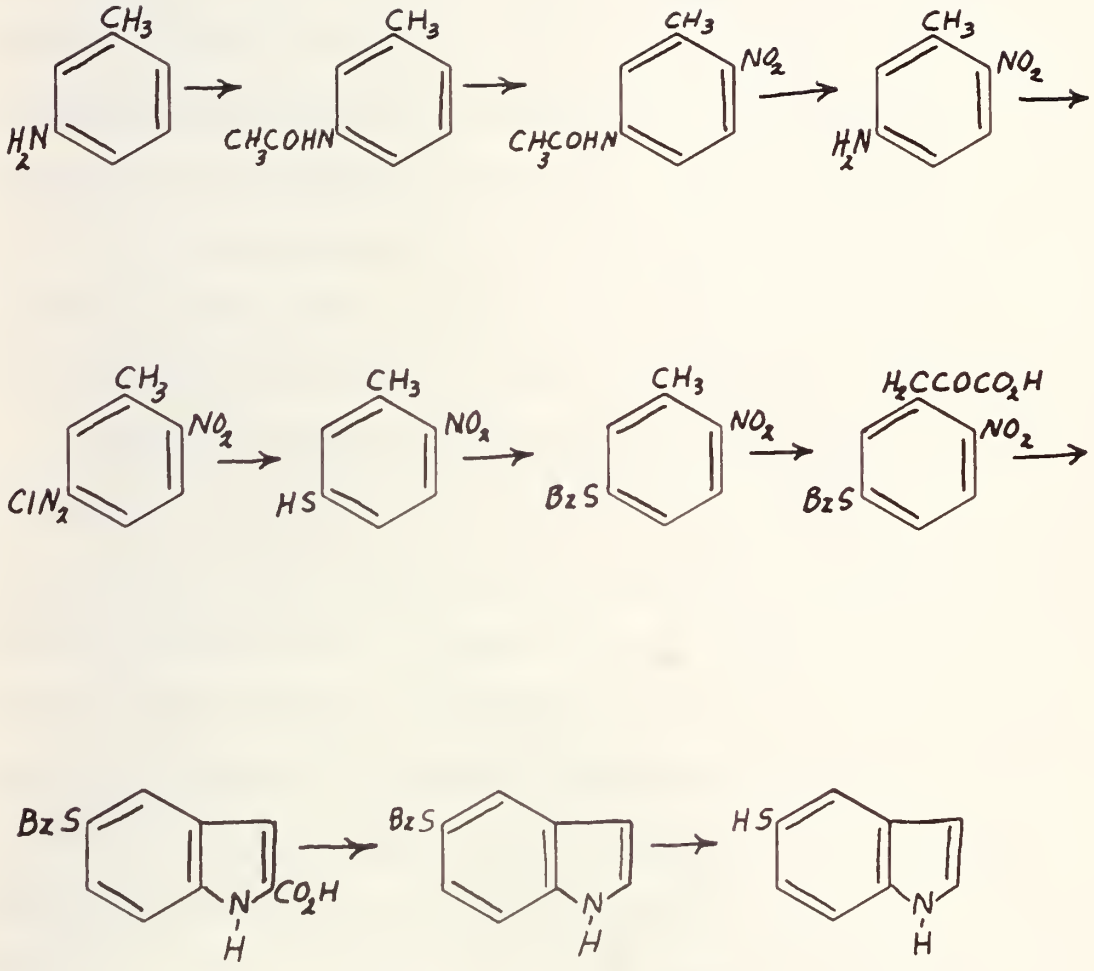
$$(R_2S + 2Na \longrightarrow RS^- + R^- + 2Na^+)$$

The outer shell of sulfur is believed to be able to accommodate more than eight electrons, while oxygen cannot.

DuVigneaud, et al. (45) have prepared cysteine by debenzylation of S-benzyl cysteine with sodium in liquid ammonia. They have found this medium to be quite useful for benzylation as well; e.g., they reduced cystine to cysteine and benzylated the latter by addition of benzyl-chloride to the reaction mixture. On the other hand, Plieninger (33) has treated indole with sodium and benzyl chloride in liquid ammonia for the purpose of N-benzylation, but he was not able to debenzylate the resulting compound using sodium and liquid ammonia. Schorigin (39) has shown that the phenyl group is more strongly attached to the sulfur than is the benzyl group. He heated phenybenzylsulfide in a sealed tube with sodium wire for thirty-six hours and found that toluene was formed to the exclusion of benzene.

It was found that 6-mercaptoindole may be prepared from 6-benzylmercaptoindole by means of sodium in liquid ammonia, using the blue coloration imparted to the solution by excess sodium as the end-point of the reaction. The = N-H group of the indole emerges from the reaction unchanged.

The preparation of 5-mercaptoindole was accomplished by essentially the same route as that used for the 6-isomer via the following route:



Since we were unable to obtain the 2-nitro-5-benzyl-mercaptophenylpyruvic acid as a solid, and since distillation probably would have led to decomposition, it was used without further purification. That it actually was a phenylpyruvic

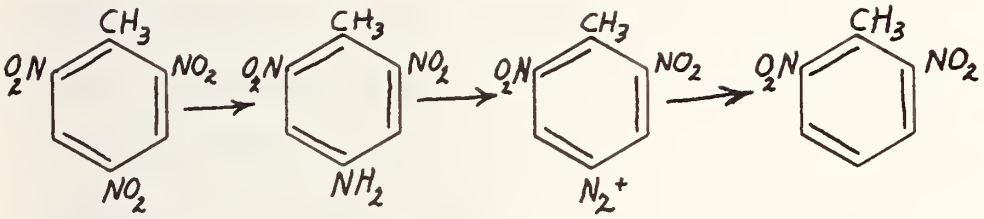
acid was shown by the positive tests which it gave for this structure, i.e. - a green solution with alcoholic ferric chloride and a red solution with sodium hydroxide.

It was of interest to note that the amount of dilute ammonium hydroxide required to dissolve 2-carboxy-5-benzylmercaptoindole was considerably less than that required for the 6-benzylmercapto isomer. The latter necessitated many extractions with hot dilute ammonium hydroxide before the major portion was dissolved, whereas, the former was taken up by one portion of warm dilute ammonia.

Attempts to prepare 4-mercaptoindole have not been successful as yet. In order to apply Reissert's method to the synthesis of this compound, it is necessary to prepare 2-nitro-6-aminotoluene. A number of routes have been tried, but none have yielded a satisfactory product. One approach was the preparation of 2,6-dinitrotoluene which may be reduced with ammonium sulfide to give 2-nitro-6-aminotoluene (20). Cunerth's method (14) for the preparation of the dinitrotoluene was tried, but separation of the isomers obtained was not effected by crystallization and distillation was considered to be too dangerous.

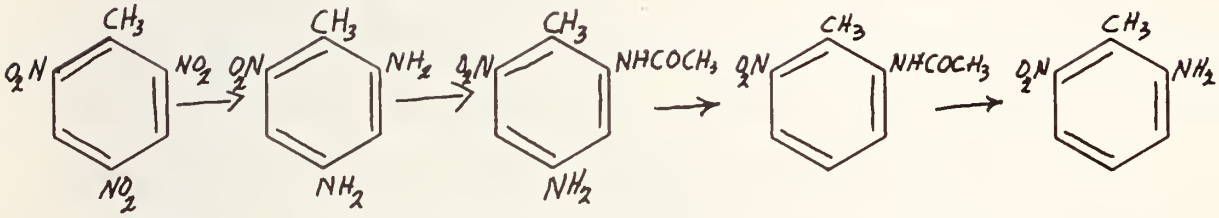
It was then thought that the desired dinitrotoluene might be prepared via the following scheme, involving reduction

of 2,4,6-trinitrotoluene to yield 2,6-dinitro-4-aminotoluene and then removal of the 4-amino group via diazotization.



Cohen and Dakin (11) and Cohen and McCandlish (13) have reduced 2,4,6-trinitrotoluene with hydrogen sulfide in absolute methanol to which a small amount of concentrated ammonium hydroxide was added. This was tried but the results were unsatisfactory. The product of the reaction was difficult to purify and the yield was low. Parkes and Farthing (31) say that this is due to "the large amount of alkali used as catalyst, which has an adverse effect by producing coloured complexes with T.N.T. and by interfering with intermediate reduction products. Further, poly-component systems of molecular compounds may be formed which, along with impurities normally resulting from an organic reaction, make isolation of products difficult."

Parkes and Farthing have prepared 2-nitro-6-aminotoluene by a route beginning with Ruggli and Zaeslin's (36) reduction of 2,4,6-trinitrotoluene to 2,4-diamino-6-nitrotoluene. This involves saturating absolute ethanol with ammonia and then hydrogen sulfide and treating the trinitrotoluene with the resulting mixture. Parkes and Farthing subjected the diamino compound to the following series of reactions including, protection of the 2-amino group by acetylation, diazotization and removal of the 4-amino group and hydrolysis to yield 2-amino-6-nitrotoluene.



While Ruggli and Zaeslin's reduction was being studied, further information came to light concerning the acetylation of the 2-amino-group. Foster, Rosicky and Niemann (18) questioned Parkes and Farthing's assignment of the acetyl group to the 2-amino position. The former authors prepared 2,4-diamino-6-nitro-toluene from 2,4,6-trinitrotoluene by

Ruggli and Zaeslin's method and acetylated this by Parkes and Farthing's method. Deamination followed by hydrolysis gave a compound which had a melting point indicating that it was 2-nitro-4-aminotoluene (78°). On the other hand, Parkes and Farthing obtained a compound with a melting point which indicated that it was 2-nitro-6-aminotoluene (90°). Therefore, it is to be assumed that Parkes and Farthing acetylated the 2-amino-group, whereas, Foster, et al., acetylated the 4-amino-group. However, the confusing thing is that they, ostensibly, used the same methods.

Foster and co-workers prepared 2-nitro-4-aminotoluene by a different method of reduction of 2,4,6-trinitrotoluene in which the p-nitro-group is converted to the amine. Acetylation of the p-amino-group and reduction of one of the nitro-groups yielded a compound which did not depress the melting point of the compound obtained by the acetylation of 2,4-diamino-6-nitrotoluene. Deamination and hydrolysis as before gave 2-nitro-4-aminotoluene.

Since Parkes and Farthing's preparation of 2-nitro-6-aminotoluene has been questioned, it has been decided to prepare this compound by another route. Foster and co-workers prepared 2-nitro-6-aminotoluene by reducing the p-nitro-group of 2,4,6-trinitrotoluene, removing the resulting amino-group by deamination and reducing the 2,6-dinitrotoluene, thus obtained,

to 2-nitro-6-aminotoluene. This method is currently under investigation.

Another route to 2-nitro-6-benzylmercaptotoluene has been investigated, viz. replacement of a bromine atom by the thiol group followed by S-benzylation. As mentioned before, a number of workers have prepared thiols by the replacement of an active bromine or chlorine atom using sodium or potassium hydrosulfide or thiourea. Therefore, 2-bromo-6-nitrotoluene (22) was treated with potassium hydrosulfide in refluxing sec. butanol and the reaction mixture treated with sodium hydroxide and benzyl chloride. Fractional distillation of the ether extract yielded a colourless compound which proved to be dibenzyl disulfide. After the disulfide was removed as completely as possible, the residue was again fractionally distilled but no satisfactory product was obtainable. Column chromatography gave no better results. The 2-bromo-6-nitrotoluene treated with potassium hydrosulfide in methanol was equally as unsatisfactory.

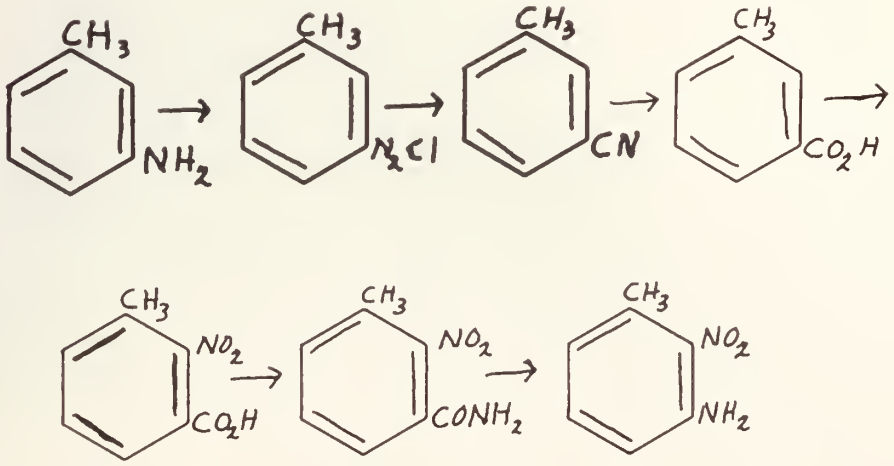
It was then decided to try to prepare 2-nitro-4-benzylmercaptotoluene, which is available by another route, by this method to see if a compound could be obtained whose characteristics were known. This, too, was unsuccessful.

Since dibenzyldisulfide was formed in considerable quantity in these reactions, it was thought that it might be

hindering the purification of the desired product. The formation of the disulfide could be prevented by omitting the benzylation until the thiol had been freed of excess potassium hydrosulfide. 2-Nitro-4-bromotoluene was treated with potassium hydrosulfide in refluxing methanol as well as in the monoethyl ether of ethylene glycol. No base soluble material was obtained in either reaction.

With respect to the synthesis of the 7-mercaptoindole, there has been found what might be a satisfactory route to 2-nitro-3-aminotoluene which, when converted to 2-nitro-3-benzylmercaptotoluene and subjected to the Reissert indole synthesis, should afford the 7-isomer.

Tomisek, et al. (43) prepared 2-nitro-3-aminotoluene in the following manner:



This involves the preparation of m-tolunitrile which is an adaptation of the reaction on o- and p-toluidines to give o- and p-tolunitriles (10). The nitrile is hydrolysed to m-toluic acid in 18N sulfuric acid and the method of Müller (30) is employed to convert this to 2-nitro-m-toluic acid. The latter is converted to the amide by the method of Geerling and Wibaut (19) which is a modified method of Jürgens (26). 2-Nitro-3-aminotoluene is obtained by a Hoffman degredation of the amide using a modification of Hoogewerff and van Dorp (23). Up to the time of writing, this series of reactions has been completed to the amide.

EXPERIMENTAL

2-Nitro-4-aminotoluene. This compound was prepared in excellent yield by the method of Cohen and Dakin (12) for 2-amino-4-nitrotoluene.

2-Nitro-4-benzylmercaptotoluene. The method of Bennett and Berry (4) was employed to convert the amino group to the thiol.

Fifty-four grams (0.282 moles) of 2-nitro-4-aminotoluene was dissolved by heat in 750 ml. of water containing 150 ml. of concentrated hydrochloric acid. The resulting solution was filtered and cooled to 10° in a salt-ice bath. Diazotization was accomplished by the dropwise addition at 10° of a sodium nitrite solution (26.5 g. in sufficient water) until starch-iodide test-paper showed the persistance of free nitrous acid for 5-10 minutes. This mixture was kept in ice for about 30 minutes, and the liquid was then filtered into a solution of 75 g. of potassium ethyl xanthate and 150 g. of borax in 750 ml. of water at 70-75°. (It is necessary to add the diazo-solution cautiously, otherwise an explosive evolution of gas may ensue.) The mixture was heated on a steam-bath until effervescence ceased. The cooled, precipitated oil was extracted with ether, the ether

washed with water, dried over anhydrous sodium sulfate and removed by distillation. The residual xanthogenic ester was hydrolysed by refluxing under nitrogen with a solution consisting of 20 g. of sodium in 200 ml. of ethanol to which 40 ml. of water was added. Refluxing was continued until a test-portion was completely soluble in water. The solution, mixed with an equal volume of water, was poured into a separatory funnel which previously had been flushed with nitrogen. Benzylchloride (50 g.) was added and the mixture was shaken vigorously for 5 minutes. An additional 10 g. of benzyl chloride was added and shaking was continued for 5 minutes longer. An alkaline (litmus) condition was maintained during the shaking by appropriate addition of 2.5N sodium hydroxide. The cooled solution was extracted with ether, the ethereal extract washed with water and dried over anhydrous sodium sulfate. The ether was removed by distillation and the oil remaining was fractionally distilled under vacuum to yield 29 g. (34%) of 2-nitro-4-benzylmercaptotoluene, b.p. 143° at 0.23 m.m., m.p. 78°.

Anal. Calcd. for $C_{14}H_{13}O_2NS$: S,12.37

Found: S, 12.23.

2-Nitro-4-benzylmercaptophenylpyruvic acid. To a solution of 8.2 g. (0.355 mole) of sodium in 170 ml. of anhydrous ethanol were added 52 g. (0.355 mole) of diethyl oxalate and 73 g. (0.355 mole) of 2-nitro-4-benzylmercaptotoluene. The solution,

which became dark-red in colour, was re-fluxed for one hour, cooled, diluted with twice its own volume of water, extracted three times with ether and made acidic to Congo Red with concentrated hydrochloric acid. Air was blown through the oily solution to remove residual ether whereupon crystals formed, which were removed by filtration, dissolved in dilute ammonium hydroxide and reprecipitated with contentrated hydrochloric acid. After recrystalization from alcohol-water, 66 g. (80%) of 2-nitro-4-benzylphenylpyruvic acid, m.p. 166-167° dec., was obtained. Starting material (9 g.) was recovered from the ethereal extract.

Anal. Calcd. for $C_{16}H_{13}O_5$ NS: S, 9.69

Found: S.

2-Carboxy-6-benzylmercaptoindole. The method of Blaikie and Perkin (5) was employed. To a solution of 15 g. (0.045 mole) of 2-nitro-4-benzylmercaptophenylpyruvic acid in 63 ml. of concentrated ammonium hydroxide (sp. gr. 0.88) made up to 90 ml. with water, was added a hot solution of 83.4 g. (0.3 mole) of ferrous sulfate heptahydrate in 210 ml. of water. Reduction was instantaneous and the black mixture was heated on a water bath for half an hour and then refluxed for the same length of time. The hot solution was filtered and the black sludge of ferric hydroxide was extracted repeatedly with boiling dilute ammonium hydroxide until a test-portion gave only a slight

milkiness on acidification. The extractions were acidified to Congo Red with concentrated hydrochloric acid, cooled well in ice and filtered. The crude product was washed with water and suspended in very dilute hydrochloric acid containing some barium chloride to remove sulfate and extracted with ether. The ether extract was washed twice with water, dried over anhydrous sodium sulfate and evaporated to dryness. The solid remaining was extracted repeatedly with boiling dilute ammonium hydroxide. The extracts were combined, acidified, cooled, filtered and the precipitate washed with water. 2-Carboxy-6-benzylmercaptoindole (8 g., 62%), m.p. 215°, was obtained.

Anal. Calcd. for $C_{16}H_{13}O_2NS$: S, 11.35.

Found: S, 11-32.

6-Benzylmercaptoindole. 2-Carboxy-6-benzylmercaptoindole (32 g., 0.113 mole) and 5 g. of copper chromite catalyst (27) were heated for 16 hours at 200° in 320 ml. of redistilled, synthetic quinoline. The cooled quinoline solution was acidified with 3N hydrochloric acid, and then extracted 4 times with ether. The extracts were combined, filtered to remove suspended catalyst, washed once with 3N hydrochloric acid, twice with saturated sodium bicarbonate solution, twice with water and then dried over anhydrous sodium sulfate. The ether was removed, and the residue was extracted with hot ethanol, treated with norite, reduced in volume and allowed to cool. A precipitate was formed

which was removed, and the filtrate further reduced in volume yielding another crop of the product. The combined precipitates, after crystallization from alcohol-water afforded 18 g. (67%) of 6-benzylmercaptoindole, m.p. 106.5-107°.

Anal. Calcd. for $C_{15}H_{13}NS$: S, 13.41.

Found: S, 13.32.

6-Mercaptoindole. The method of du Vigneaud and co-workers was used (45). Liquid ammonia (125 ml.) was placed in a 50 X 150 m.m. test-tube supported in a Dewar flask by means of a cork. To this was added 5 g. (0.021 mole) of 6-benzyl-mercaptoindole followed by small pieces of sodium metal stirred into the ammonia until a blue colour of 5-10 minutes persistance was obtained. Excess sodium was then destroyed by the addition of ammonium iodide until the blue colour disappeared. The test-tube was removed from the Dewar flask, and the ammonia was boiled off under a blanket of purified nitrogen in a fume hood. (The nitrogen was purified by bubbling through a solution of chromous chloride and then dried over sodium hydroxide pellets.) Residual ammonia was removed by alternately evacuating and flushing the test-tube with nitrogen. Distilled water (125 ml.), which had been boiled and cooled, was added to the test-tube, and sufficient 3N hydrochloric acid added to acidify the solution, which was then cooled and filtered quickly under a blanket of nitrogen. The solution obtained after treatment of the precipitate

with dilute sodium hydroxide was filtered and acidified with 3N hydrochloric acid. The solution was cooled and filtered, the precipitate was washed with cold, boiled, distilled water and dried in an evacuated dessicator over phosphorous pentoxide. 6-Mercaptoindole, 1.5 g. (49%), m.p. 70-71°, was obtained, and was stored in a vial under nitrogen.

Anal. Calcd. for C_8H_7NS: S, 21.48.

Found: S, 21.30.

N-Acetyl-m-toluidine. The method as given by Fieser (15) proved satisfactory.

2-Nitro-5-N-acetylaminotoluene. The preparation followed in detail that given by Fieser (16). The product obtained proved to be a mixture of acetylated and unacetylated 2-nitro-5-aminotoluene.

2-Nitro-5-aminotoluene. The crude product from the nitration was hydrolysed in 20 g. batches in a mixture of 1200 ml. of concentrated hydrochloric acid and water (1:1) containing enough ethanol to dissolve the solid when hot. The solution was refluxed for one hour, cooled and the acid neutralised with solid sodium carbonate. The precipitate was removed by filtration and extracted with boiling dilute hydrochloric acid. The combined extracts were basified with sodium carbonate, filtered and the precipitate washed well with water. The material which was not soluble in

hydrochloric acid was hydrolysed as above in twenty-gram batches. From 180 g. of the mixture of acetylated and unacetylated material, there was obtained 103 g. of 2-nitro-5-aminotoluene, m.p. 129-130°, lit. 133-135°.

2-Nitro-5-benzylmercaptotoluene. The same method was used in the preparation of this compound as was used in the synthesis of 2-nitro-4-benzylmercaptotoluene. From 54 g. of 2-nitro-5-aminotoluene, there was obtained 26.5 g. (30%) of 2-nitro-5-benzylmercaptotoluene, m.p. 55.5-57°.

Anal. Calcd. for $C_{14}H_{13}O_2NS$: S, 12.37.

Found: S, 12.28.

2-Nitro-5-benzylmercaptophenylpyruvic acid. The method employed in the synthesis of 2-nitro-4-benzylmercaptophenylpyruvic acid was used. From 45 g. of 2-nitro-5-benzylmercaptotoluene, there was obtained an oil which would not crystalize. Therefore it was taken up into dilute ammonium hydroxide and reprecipitated with concentrated hydrochloric acid. The oil was extracted with ether, the ether was dried and the product after evaporation of the ether, was subjected to the next reaction. Starting material to the extent of 19.5 g. was recovered.

2-Carboxy-5-benzylmercaptoindole. This compound was prepared in the same manner as its 6-isomer by the reduction of the oil from the preceeding reaction. The carboxyindole was extracted from the black sludge, treated to remove sulfate ion, dissolved

in ammonium hydroxide, treated with norite and precipitated with concentrated hydrochloric acid. 2-Carboxy-5-benzylmercaptoindole (15.2 g., 55% on the basis of 25.5 g. of 2-nitro-5-benzylmercaptotoluene employed) m.p. 210.5-211.5° dec.

Anal. Calcd. for $C_{16}H_{13}O_2NS$: S, 11.35.

Found: S, 11.4.

5-Benzylmercaptoindole. 2-Carboxy-5-benzylmercaptoindole (15g.) was decarboxylated in the same manner as its 6-isomer by heating in quinoline with copper chromite catalyst for 11 hours at 200-210°. 5-Benzylmercaptoindole (6.6 g., 52%), m.p. 75-74°, was obtained.

Anal. Calcd. for $C_{15}H_{13}NS$: S, 13.41

Found: 13.62.

5-Mercaptoindole. 5-Benzylmercaptoindole (4 g.) was debenzylated with sodium in liquid ammonia in the same manner as its 6-isomer. 5-Mercaptoindole (1.5 g., 60%), m.p. 75-76°, was obtained.

Anal. Calcd. for C_8H_7NS: S, 21.48.

Found: S, 21.48.

2-Nitro-3-aminotoluene. Directions for the preparation of this compound from m-toluidine are given by Tomisek, et al. (43).

SUMMARY

The synthesis of 5- and 6-mercaptoindoles has been accomplished via the Reissert indole synthesis. This involved the preparation of the 2-nitro-4- and 5-benzylmercaptotoluenes from the 2-nitro-4- and 5-aminotoluenes, respectively. The benzylmercaptotoluenes were condensed with diethyl oxalate and the resulting phenylpyruvic acids were cyclized to the carboxyindoles. The latter were decarboxylated and debenzylated to yield the 6- and 5-mercaptoindoles.

A number of routes to prepare 2-nitro-6-benzylmercaptotoluene, which might be converted to 4-mercaptoindole, were unsatisfactory.

The preparation of 2-nitro-3-aminotoluene, from which 7-mercaptoindole might be prepared, has been partially completed.

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